

Case Report

Vanishing white matter disease: A diagnostic challenge on magnetic resonance imaging in a pediatric patient

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ABSTRACT

Vanishing white matter disease is a rare autosomal recessive leukodystrophy characterized by progressive neurological deterioration and episodes of acute worsening triggered by minor stressors. We report the case of a 7-year-old boy presenting with transient neurological deficits following mild head trauma. Brain magnetic resonance imaging (MRI) revealed diffuse and symmetric white matter abnormalities with progressive cystic degeneration. Genetic testing identified a homozygous pathogenic variant in the *EIF2B5* gene, confirming the diagnosis. Early recognition of characteristic MRI findings is crucial to guide management and avoid precipitating factors.

Keywords: Vanishing white matter disease, Leukodystrophy, Pediatric neuroradiology, Magnetic resonance imaging, *EIF2B* gene

INTRODUCTION

Vanishing white matter disease (VWM) is a rare autosomal recessive leukodystrophy characterized by progressive neurological deterioration and episodes of acute worsening triggered by minor stressors. It is caused by pathogenic variants in the *EIF2B1–EIF2B5* genes, which impair the cellular stress response and predominantly affect oligodendrocytes and astrocytes. Magnetic resonance imaging (MRI) plays a pivotal role in early recognition, as it demonstrates a characteristic pattern of diffuse and symmetric white matter involvement with progressive rarefaction and cystic degeneration. Early identification of these imaging findings is essential to prompt genetic confirmation and guide clinical management.

CASE REPORT

We report the case of a 7-year-old boy with no relevant past medical history. He was born from a first pregnancy, delivered preterm by cesarean section at 36 weeks of gestation due to fetal bradycardia, without subsequent neonatal complications or developmental delay during early childhood.

The patient was referred to our medical center after sustaining a fall from standing height, without apparent precipitating factors. Following mild head trauma, he developed transient neurological deterioration, predominantly characterized by decreased muscle strength in the upper and lower limbs, resulting in impaired ambulation. No loss of consciousness or seizures was reported at the time of presentation.

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Given the acute neurological symptoms, neuroimaging studies were performed. Brain magnetic resonance imaging (MRI) demonstrated findings highly suggestive of vanishing white matter disease, characterized by diffuse and symmetric involvement of the cerebral white matter. The affected areas showed abnormal signal intensity with marked rarefaction and regions compatible with cystic degeneration [Figure 1]. No significant contrast enhancement or diffusion restriction was identified.

Based on the characteristic imaging findings, genetic testing was requested to confirm the suspected diagnosis. A next-

generation sequencing panel targeting genes associated with leukodystrophies and leukoencephalopathies, complemented by copy number variation analysis, identified a homozygous pathogenic variant in the *EIF2B5* gene (NM_003907.3): c.338G>A (p.Arg113His). A follow-up MRI performed one year later demonstrated progression of cystic degeneration within the periventricular white matter [Figure 2]. These results were consistent with the diagnosis of evanescent (vanishing) white matter disease.

Vanishing white matter disease is a rare autosomal recessive leukodystrophy caused by pathogenic variants in the

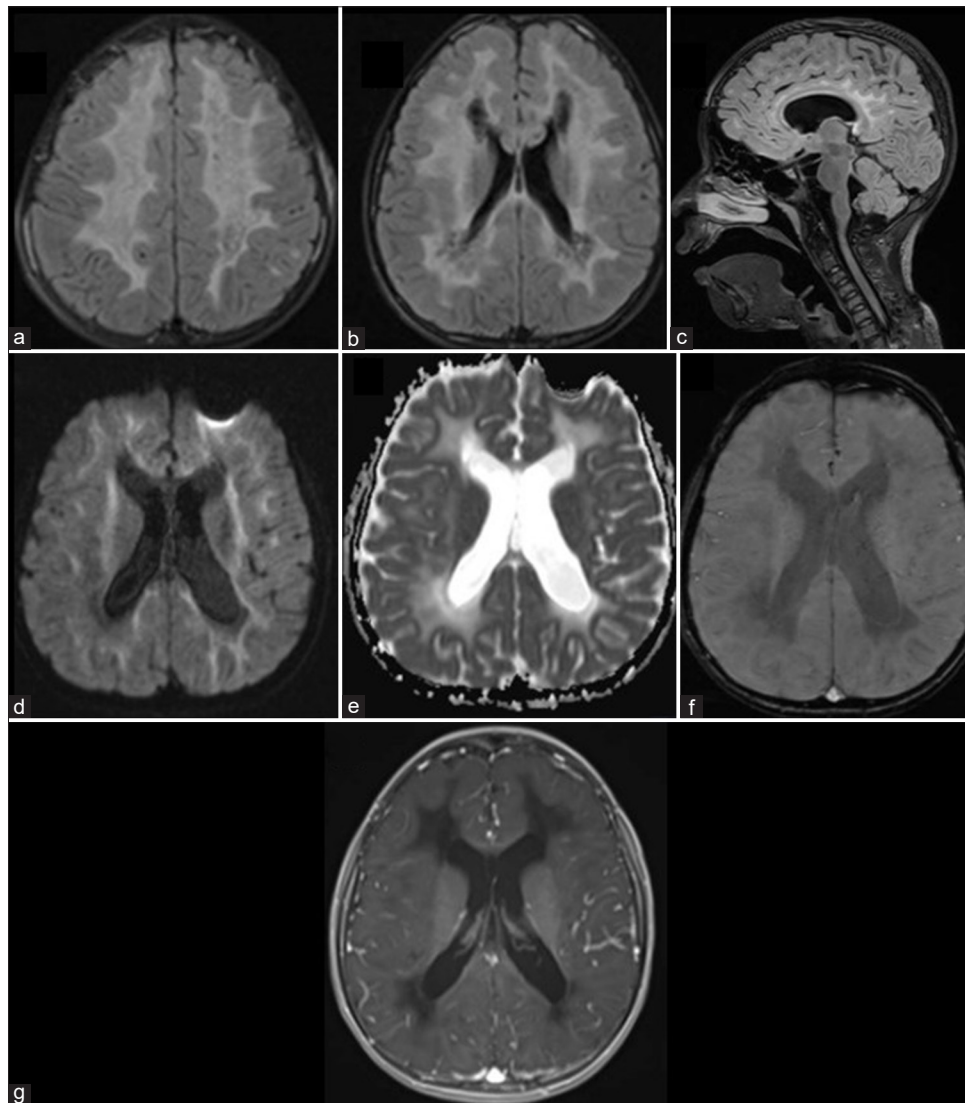


Figure 1: (a and b) Axial fluid-attenuated inversion recovery (FLAIR) images at different levels. (c) Midline sagittal FLAIR image shows symmetrical bilateral periventricular hyperintensity of the white matter and the inner border of the corpus callosum, associated with incipient hypointense areas within the posterior periventricular white matter. (d) Diffusion-weighted imaging (DWI) and (e) apparent diffusion coefficient (ADC) maps show no diffusion restriction. (f) Gradient echo (GRE) sequence shows no evidence of hemorrhage or calcification. (g) Post-contrast axial T1-weighted image shows no areas of enhancement.

EIF2B1–EIF2B5 genes, which encode the five subunits of the eukaryotic initiation factor 2B (eIF2B).^[1,2] This factor plays a crucial role in the regulation of protein synthesis under conditions of cellular stress. Mutations in these genes result in impaired stress response mechanisms, particularly affecting oligodendrocytes and astrocytes, leading to progressive degeneration of cerebral white matter.^[2,5,6]

Clinically, the disease is characterized by chronic progressive neurological deterioration, often punctuated by episodes of acute worsening triggered by minor stressors such as infections, fever, or mild trauma.^[1,2] Common manifestations include muscle weakness, spasticity, gait instability, loss of previously acquired motor skills, cerebellar signs, and cognitive impairment.^[1,4] The transient neurological decline observed in our patient following mild head trauma is consistent with the known clinical behavior of this disorder.^[2,3]

MRI is the cornerstone of diagnosis, as it demonstrates a highly characteristic pattern.^[1,7] Typical findings include diffuse, symmetric white matter abnormalities with progressive rarefaction and cystic degeneration, resulting in signal intensity similar to cerebrospinal fluid on T2-weighted and fluid-attenuated inversion recovery images.^[1,2,7] Relative preservation of the subcortical U-fibers is an important

diagnostic clue that helps differentiate vanishing white matter disease from other leukodystrophies and inflammatory white matter disorders.^[7,8]

The differential diagnosis includes metachromatic leukodystrophy, Krabbe disease, X-linked adrenoleukodystrophy, and hypomyelinating leukodystrophies, as well as acquired inflammatory or infectious leukoencephalopathies.^[7] However, these entities typically demonstrate additional imaging features such as contrast enhancement, basal ganglia involvement, diffusion restriction, or asymmetric distribution, which were absent in this case.^[7,8]

Currently, management remains primarily supportive, focusing on symptomatic treatment and strict avoidance of triggering factors that may precipitate neurological deterioration.^[1,2] Although no curative therapy is available, ongoing research is exploring potential targeted treatments, including modulation of the integrated stress response and inhibition of glycogen synthase kinase-3 β activity.^[5,9,10]

This case highlights the critical role of MRI in the early recognition of vanishing white matter disease and emphasizes the importance of correlating imaging findings with clinical presentation to guide appropriate diagnostic workup and management.

Table 1: Differential diagnosis.

Entity	Clinical features	MRI findings	Key distinguishing features
Vanishing white matter disease	Progressive neurological decline with episodic deterioration triggered by stress (minor trauma, infections, fever). Childhood onset.	Diffuse, symmetric cerebral white matter involvement with progressive cystic degeneration; signal intensity approaching CSF on T2/FLAIR; relative sparing of U-fibers in early stages.	Stress-related deterioration, characteristic cavitating pattern, confirmation by <i>EIF2B</i> mutations.
Metachromatic leukodystrophy	Progressive psychomotor decline, peripheral neuropathy, cognitive impairment.	Symmetric periventricular white matter abnormalities, often with tigroid pattern; no extensive cystic degeneration.	Reduced arylsulfatase A activity; peripheral nervous system involvement.
X-linked adrenoleukodystrophy	Affects males; behavioral changes, cognitive decline, adrenal insufficiency.	Predominantly parieto-occipital white matter lesions with peripheral contrast enhancement during active inflammation.	Posterior predominance, inflammatory enhancement, elevated very long-chain fatty acids.
Chronic hypoxic–ischemic encephalopathy	History of perinatal hypoxia; static or slowly evolving neurological deficits.	Periventricular white matter injury without diffuse progressive cavitation.	Clear perinatal history; non-progressive imaging pattern.
Pediatric multiple sclerosis	Relapsing neurological symptoms, focal deficits.	Multifocal, asymmetric white matter lesions involving periventricular and juxtacortical regions; possible contrast enhancement.	Dissemination in time and space; oligoclonal bands in CSF.
Toxic or metabolic leukoencephalopathy	History of toxin exposure, chemotherapy, or metabolic disturbance.	Diffuse white matter signal abnormalities, usually non-cavitating and potentially reversible.	Clinical context of exposure; different temporal evolution.
Canavan disease	Early infantile onset, macrocephaly, severe developmental delay.	Diffuse white matter T2 hyperintensity without cavitation; basal ganglia involvement.	Elevated N-acetylaspartate; neonatal or early infantile presentation.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, CSF: Cerebrospinal fluid

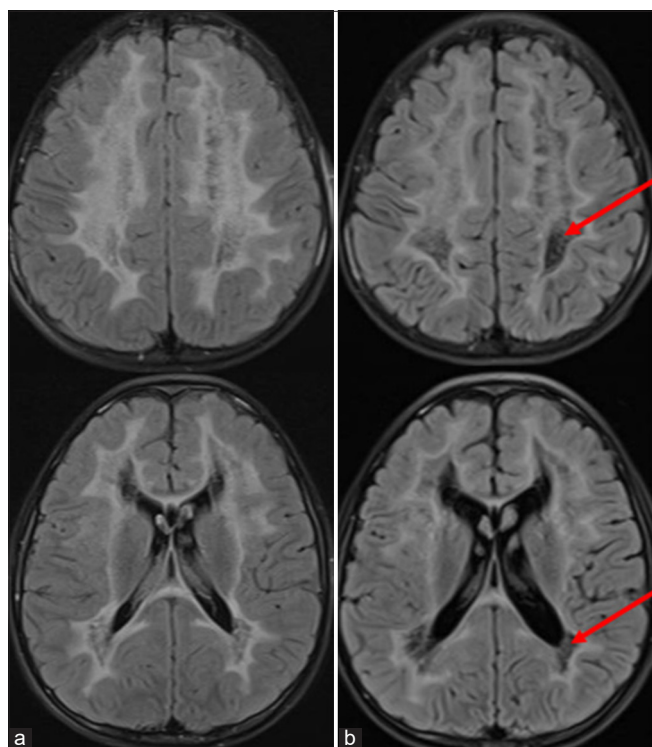


Figure 2: Comparative brain magnetic resonance imaging (MRI). (a) Initial axial fluid-attenuated inversion recovery (FLAIR) image demonstrates periventricular white matter hyperintensity with incipient hypointense areas, predominantly in the posterior periventricular region. (b) Axial FLAIR image obtained one year later demonstrates progression of hypointense areas within the white matter, consistent with cystic degeneration (red arrows).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for this case is mentioned in Table 1 under differential diagnosis.

CONCLUSION

Vanishing white matter disease should be considered in pediatric patients presenting with transient or stress-related neurological deterioration. Recognition of the characteristic MRI pattern, particularly diffuse symmetric white matter involvement with progressive cystic degeneration, is essential to prompt timely genetic confirmation and guide counseling and preventive management strategies.

TWO TEACHING POINTS

Evanescent (vanishing) white matter disease may present with nonspecific or transient neurological symptoms, and minor stressors such as mild head trauma or infections can precipitate acute neurological deterioration, leading to the initial clinical recognition of the disease.

Brain MRI is central to the diagnosis, as the presence of extensive periventricular white matter involvement with

cystic degeneration is highly suggestive and should prompt early genetic testing to confirm the diagnosis and guide counseling and management.

MCQs

- Which clinical feature is most characteristic of vanishing white matter disease?
 - Acute neurological deterioration triggered by minor trauma or infections
 - Early onset adrenal insufficiency
 - Progressive peripheral neuropathy as the initial manifestation
 - Recurrent seizures as the predominant symptom

Answer Key: a

Explanation:

Vanishing white matter disease is characterized by episodes of acute neurological worsening precipitated by minor stressors such as mild head trauma, infections, or fever, which is a key distinguishing clinical feature.

- Which MRI finding is most suggestive of vanishing white matter disease?
 - Asymmetric multifocal white matter lesions with contrast enhancement
 - Predominantly parieto-occipital white matter involvement with inflammatory changes
 - Diffuse symmetric white matter involvement with progressive cystic degeneration
 - Isolated basal ganglia abnormalities with restricted diffusion

Answer Key: c

Explanation:

The hallmark MRI feature of vanishing white matter disease is diffuse and symmetric cerebral white matter involvement with progressive rarefaction and cystic degeneration, often showing signal intensity similar to cerebrospinal fluid on T2-weighted and FLAIR images.

- Vanishing white matter disease is caused by pathogenic variants in genes encoding:
 - Myelin structural proteins
 - Peroxisomal enzymes involved in fatty acid metabolism
 - Subunits of the eukaryotic initiation factor 2B (eIF2B)
 - Mitochondrial respiratory chain complexes

Answer Key: c

Explanation:

Mutations in the *EIF2B1–EIF2B5* genes, which encode subunits of the eukaryotic initiation factor 2B, impair the cellular stress response and underlie the pathophysiology of vanishing white matter disease.

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Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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